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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/817,525	04/01/2004	Tamara Byk	69222-A/JPW/DNS	4877

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/817,525	BYK ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *4-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-3, in the response filed 1/4/07 is acknowledged. Applicant requested reconsideration of the restriction requirement insofar as it involves group IV because claims of group IV all depend directly or indirectly from claim 1, and the method or process of group IV necessarily includes all steps of claim 1, and a search of these claims can be made without serious burden. This is not found persuasive because stem cells used by the method of group IV may be produced by a different method, and indistinguishable from stem cells made by instant claim 1. Thus, it is maintained that each of the Inventions requires a separate search status and consideration. The inventions are mutually exclusive and independent methods for cultivating stem cells or for treating a patient using stem cells, the searches would not be co-extensive. M.P.E.P. states, "FOR PURPOSES OF THE INITIAL REQUIREMENT, A SERIOUS BURDEN ON THE EXAMINER MAY BE PRIMA FACIE SHOWN IF THE EXAMINER SHOWS BY APPROPRIATE EXPLANATION OF SEPARATE CLASSIFICATION, OR SEPARATE STATUS IN THE ART, OR A DIFFERENT FIELD OF SEARCH AS DEFINED IN MPEP § 808.02". Therefore, it is maintained that these inventions are distinct due to their divergent subject matter. Further search of these inventions is not co-extensive, as indicated by the separate classifications. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the

Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

The species election drawn to hematopoietic stem cells is acknowledged. Upon search and consideration, the species election requirement is withdrawn.

Claims 1-26 are pending, however, claims 4-26 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-3 are under current examination.

Specification

The disclosure is objected to because of the following informalities: The specification contains nucleic acid and amino acid sequences that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason set forth as follows: The CRF Sequence listing indicates a total of 313 amino acids for SEQ ID No: 2, while figure 1 of the specification in the file indicates a total of 264 amino acids for SEQ ID No: 2. Applicant must resolve the contradiction. In the case the error is in the sequence listing, applicant should provide a substitute paper copy and/or a substitute computer readable copy of the Sequence Listing and a new statement that the content of the paper and computer

readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). A full response to this Office action must include a complete response to the requirement for a new Sequence Listing.

Claim Objections

Claim 1 is objected to because of an undefined acronym "sFRP1".

Claim 1 is objected to because it encompasses multiple inventions. Upon election of an invention for examination in this application, claims should be amended so that they only read on the elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731,

737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims are directed to a process for inducing proliferation of stem cells comprising administering to cultured stem cells sFRP1 polypeptide, preferably hematopoietic or embryonic stem cells. The specification teaches sFRPs may function in vivo to modulate Wnt signaling or alternatively as novel ligands for as yet unidentified receptors, while Wnt pathway is involved in the expansion of hematopoietic cells. The specification speculated since sFRP1 is a biphasic regulator of Wnt signaling (i.e. blocking Wnt activity at high concentration and opposite effect at low concentration), sFRP1 may be used in the context of stem cell expansion or proliferation (Specification, page 6-7). In working example 3, the applicant examined the expression pattern of sFRP1 in different hematopoietic organs in the mouse embryo, and reports "*sFRP1 is up-regulated in the AGM from the moment HSCs begin to appear and stay up-regulated during the in vivo and ex vivo expansion of HSCs*" (Specification, page 29). The specification explains, that the AGM stands for aorta-gonado-mesonephros, the first region of long term repopulating HSCs, at the time points when HSCs proliferate most in this region at days 10.5-13.5 of embryonic age (Specification, page 8, 2nd paragraph).

These are the only evidence showing the correlation between the sFRP1 and proliferation of hematopoietic and/or embryonic stem cells. The problem is that one may not be able to extrapolate the co-incidence of the sFRP1 up-regulation and HSCs proliferation during *embryonic development* to conclude that administering sFRP1 in cultured stem cells would induce proliferation of the cultured cells *outside* of an embryo. This is because different factors control embryonic development or cell cycle processes while they are in cell culture. There is no known correlation concerning the function of growth factors between embryonic development and induction of cultured stem cell proliferation, and thus the exact role of sFRP1 on hematopoietic stem cells when administered into a cell culture is unpredictable. In fact, quite a few prior and post-filing art reported evidence contrary to what is now claimed. For example, *Weissman et al* (US 2004/0171559) teach administering sFRP1 would induce quiescence, not proliferation, in normal stem cells (e.g. claims 1, 19, and 20). In view of such, the invention does not appear to be enabled in the absence of clarification of the contradictory evidence found in the references.

Given the broadest reasonable interpretation, the claims encompass stimulating proliferation in any type of stem cells. However, the only evidence presented in the specification is the sFPR1 expression pattern in the mouse embryo during the early developmental stage of HSCs. In view of the state of the art, it was well known in the art that sFPR1 is a biphasic modulator of Wnt signaling, a family of proteins that have a variety of important functions during embryonic development including stimulating proliferation (*Uren et al*, J Biol Chem 2000;275:4374-82, IDS). The physiological effect

of sFPR1 appears to be varied in different cell types and often show tissue specificity. For example, *Bodine* (US 2004/0115195) teaches deletion of sFRP1 was found to not affect non-skeletal tissue development. *Aubert et al* (Nat Biotech 2002;20:1240-5, IDS) teach sFPR1 induce neural stem cell differentiation, not proliferation. *Lassar et al* (US 2004/0014209) teach the sFPR1 stimulate stem cell differentiation into cardiac cells. In view of such, the invention does not appear to be enabled for its full scope in the absence of clarification of the contradictory evidence found in the references. Thus, the data presented in the specification is insufficient to show that administering sFRP1 would bring all cultured stem cells from quiescent state to proliferative state, and the instant disclosure fails to meet the statutory enablement requirement.

Given the broadest reasonable interpretation, instant claims are drawn to stimulating and promoting human embryonic stem cell proliferation/expansion by administering sFRP1 into cultured ES cells. However, the specification fails to reduce to practice showing that sFRP1 indeed stimulate the in vitro expansion of ES cells. In view of the state of the art, it was well known in the art that human ES cells are extremely difficult to expand in vitro, which is a major barrier for using ES cells for therapeutic purpose. *Donovan and Gearhart* (Nat 2001 Nov;414:92-97) teach "HUMAN STEM CELL POPULATIONS PROLIFERATE MORE SLOWLY THAN THEIR MURINE COUNTERPARTS, DIFFERENTIATE MORE READILY AND THEIR CLONING EFFICIENCY IS VERY LOW" (last paragraph on page 95). *Pera et al* (J Cell Sci 2000;113:5-10) "MOST OF THE APPLICATIONS OF HUMAN ES ECLLS WILL REQUIRE CELLS TO BE GROWN AND MANIPULATED AS A RELATIVELY PURE STEM CELL POPULATION ON A LARGE SCALE, AND THE AVAILABILITY OF METHODS FOR PRODUCING AND ISOLATING SPECIFIC TYPES OF DIFFERENTIATED CELL FROM THEM. AT PRESENT, NO ONE HAS REPORTED LARGE SCALE GROWTH,

EFFICIENT CLONING OR GENETIC MANIPULATION OF HUMAN ES OR EG CELLS" (page 9, Conclusion). Thus, the factors that can stimulating proliferation of ES cells *in vitro* are unpredictable, are the subject of ongoing and intense investigations, and cannot be extrapolated from the expression pattern of the embryonic development. Thus, it is incumbent upon the applicant to provide an enabling disclosure to establish that sFRP1 stimulates the proliferation/expansion of human ES cells in vitro beyond the embryonic developmental expression. The specification fails to do so, and thus it fails to provide an enabling disclosure for what is now claimed.

In fact, a post-filing publication would challenge instant claimed invention, where *Sasai et al* claim that the sFRP1 induces differentiation (not proliferation) of ES cells into an ectodermal cell lineage (US 2006/0281179, e.g. claim 12, SEQ ID No: 8). In view of such, the invention does not appear to be enabled in the absence of clarification of the contradictory evidence found in the reference.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite because of the claim recitation, "stem cells". Given the broadest reasonable interpretation, stem cells encompass many relatively undifferentiated cells including totipotent, pluripotent, multipotent, and monopotent progenitor cells. However, the specification defines stem cells as pluripotent cells. If this is the scope of stem cells in the claims, applicant should amend the claims to reflect the scope encompassed by the recitation. This is because claims must, under modern claim practice, stand alone to define invention, since, in patentability context, claims are to be given their broadest reasonable interpretations, and since limitations are not to be read into claims from specification. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). It is not proper to read limitations appearing in the specification into the claim when these limitations are not recited in the claim. *In re Paulsen* 30 F.3d 1475, 1480, 31 USPQ 2d 1671, 1674 (Fed. Cur,1994); *Intervet America Inc. v. Kee-Vet Lab. Inc.*, 887 F.2d 1050, 1053, 12 USPQ 2d 1474, 1476 (Fed. Cir. 1989).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
February 1, 2007

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Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
February 1, 2007